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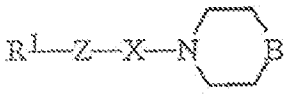
54 Novel piperidine derivatives

57 Compounds of the formula I



(I)

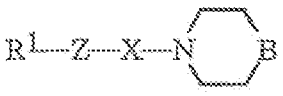
and their production and use in medicines are described.

The following information is taken from the documents submitted by the applicant

Description

The invention relates to novel piperidine derivatives, method for the production thereof and medicines containing the said compounds.

A subject-matter of the invention are compounds of the formula I

 (I)

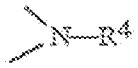
wherein

R^1 stands for substituted or unsubstituted phenyl, substituted or unsubstituted pyridine, substituted or unsubstituted naphthalene, substituted or unsubstituted quinoline, substituted or unsubstituted isoquinoline, substituted or unsubstituted indole, substituted or unsubstituted benzothiophene, substituted or unsubstituted benzofuran, substituted or unsubstituted tetrahydroquinoline, substituted or unsubstituted tetrahydroisoquinoline,

Z stands for oxygen, sulphur, SO or SO_2,

X stands for $-(CH_2)_m-CR^2R^3-(CH_2)_p$,

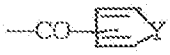
$-(CH_2)_m-CHR^2-(CH_2)_g-CHR^3-(CH_2)_p-$,

B  ,  and

m, p and g each stand for 0, 1, 2 or 3,

R^2 and R^3 are the same or different and stand for hydrogen, hydroxy, C_{1-4}-alkyl or C_{1-4}-alkoxy,

R^4 stands for hydrogen, C_{1-6}-alkyl straight-chain or branched,

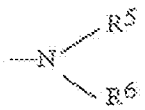


or a phenyl, benzyl, benzoyl, α-hydroxybenzyl or pyridine residue optionally substituted with C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, hydroxy, $-CF_3$ or $-O-CF_3$, and

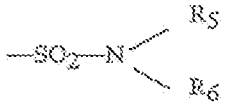
Y stands for oxygen, sulphur or –NH–,

and physiologically compatible salts and isomers thereof.

The substituent R^1 can be substituted in the same way or differently one to three times with C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, NO_2, CF_3, $-OCF_3$, hydroxy, carboxyl, C_{1-4}-alkoxycarbonyl, formyl, C_{1-4}-alkylcarbonyl, phenyl, phenoxy,



or



wherein

R^5 and R^6 are the same or different and stand for hydrogen, C_{1-4}-alkyl, phenyl, C_{1-6}-alkanoyl or jointly with the nitrogen atom a 5- or 6-membered saturated heterocycle which can be substituted one or more times with C_{1-4}-alkyl and can contain a further O, N or S atom. For example, piperidine, pyrrolidine, morpholine, thiomorpholine, piperazine, N-methylpiperazine and 2,6-dimethylmorpholine may be mentioned.

By halogen is meant fluorine, chlorine, bromine or iodine, particularly fluorine.

Alkyl means in each case a straight-chain or branched alkyl residue such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec. butyl, pentyl, isopentyl, hexyl.

The C_{1-6} alkanoyl residue is derived from straight-chain or branched aliphatic carboxylic acids such as formic acid, acetic acid, propionic acid, butyric acid, trimethylacetic acid or caproic acid.

Compounds that may be regarded as preferred are those wherein R^1 stands for substituted or unsubstituted naphthyl and Z is oxygen.

The physiologically compatible salts are derived from inorganic and organic acids. Suitable inorganic acids are for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid and suitable organic acids are for example aliphatic or aromatic mono- or dicarboxylic acids such as formic acid, acetic acid; maleic acid, fumaric acid, succinic acid, lactic acid, tartaric acid, citric acid, oxalic acid, glyoxylic acid or sulphonic acids, for example C_{1-4}-alkanesulphonic acids such as methanesulphonic acid or benzenesulphonic acids optionally substituted by halogen or C_{1-4}-alkyl, e.g. p-toluenesulphonic acid.

If an acidic function is included, salts which are suitable are the physiologically compatible salts of organic and inorganic bases such as for example the readily soluble alkali and alkaline-earth salts, as well as N-methylglucamine, dimethylglucamine, ethylglucamine, lysine, 1,6-hexadiamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxymethylaminomethane, aminopropandiol, Sovak base and 1-amino-2,3,4-butanetriol.

The compounds of formula I include all possible optical isomers and mixtures thereof.

The production of compounds of formula I and their physiologically compatible salts takes place in a known way, by

a) reacting a compound of formula II

R^1–Z–H (II),

wherein R^1 and Z have the meanings disclosed above, with a compound of formula III

A–X–N B (III),

wherein X and B have the meanings disclosed above and A represents a leaving group, or

b) reacting a compound of formula IV

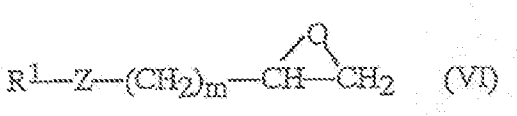
A–X–Z–R^1 (IV),

wherein X, Z and R^1 have the meanings disclosed above and A represents a leaving group, with an amine of the formula V

H–N B (V),

wherein B has the meaning disclosed above, or

c) reacting an epoxide of formula VI



(VI)

wherein R^1, Z and m have the meanings disclosed above, with an amine of the formula V

(V)

and then optionally reducing a carbonyl group or forming the physiologically compatible salts or separating the isomers.

Nucleophilic substitution of leaving group A in process variants a) and b) is undertaken by the usual methods under basic conditions in an organic solvent that is inert under the reaction conditions.

Suitable as leaving group A are halogens such as chlorine, bromine or iodine or organic sulphonic acid residues such as the residue of an alkanesulphonic acid, for example mesylate, triflate or the residue of an aromatic sulphonic acid, for example toluenesulphonic acid or bromobenzenesulphonic acid.

Suitable inert organic solvents are polar solvents such as dimethylformamide, dimethylacetamide, dimethylsulphoxide or alcohols such as ethanol, methanol or cyclic ethers such as dioxane, tetrahydrofuran, halogenated hydrocarbons, aromatic hydrocarbons or mixtures of the said solvents.

Suitable bases are inorganic and organic bases. Examples of organic bases are alkali or alkaline-earth hydroxide, alkali or alkaline-earth carbonates, alkali or alkaline-earth hydrogen carbonates or alkali or alkaline-earth alcoholates. Examples or organic bases are tertiary organic amines such as tripropylamine, triethylamine, N-alkylmorpholine, N-alkylpiperidine, Hünig's base, 1,4-diazabicyclo(2,2,2)octane and 1,5-diazabicyclo(5,4,0)undec-5-ene.

The reaction temperature can be between room temperature and the boiling point of the solvent.

The reaction according to method e) generally takes place in protic solvents such as alcohols at elevated temperature to boiling point.

The carbonyl group can be reduced with conventional reducing agents, for example with sodium borohydride, to the corresponding hydroxy compound or with triethylsilane and trifluoroacetic acid at room temperature to the methylene compound.

The compounds of formula I can be isolated from the reaction mixture and purified in a known way. Acid addition salts can be converted to the free bases in a known way and if desired the latter can be converted in a known way to physiologically compatible acid addition salts, for example by adding to the solution a concentrated solution of the desired acid.

If the compounds of formula I have one or more chiral atoms, the optically active compounds can be obtained from optically active starting compounds or in a known way from the racemates. Enantiomer separation can be undertaken for example by chromatography over optically active supports, by reacting with optically active acids and then by fractionated crystallisation.

The compounds of formula I and their physiologically compatible salts can be used as medicinal products on the basis of their functional effect on the glutamate receptor or glutamate receptor-dependent ion channel.

The pharmacological efficacy of the compounds of formula I was determined by means of the tests described below:

Male NMRI mice weighing 18-22 g were kept under controlled conditions (06:00–18:00 hrs light/dark rhythm, with free access to food and water) and randomised to groups. The groups comprised 5–16 animals. The animals were observed between 08:00 and 13:00 hrs.

AMPA was injected into the left ventricle of freely mobile mice. The applicator comprised a cannula with a stainless steel device limiting the depth of the injection to 3.2 mm. The applicator was connected to an injection pump. The injection needle was introduced perpendicular to the surface to the skull in accordance with Montemurro and Dukelow's co-ordinates. The animals were observed for up to 180 sec. until

clonic and/or tonic seizures occurred. Clonic movements lasting longer than 5 sec. were counted as seizures. The start of the clonic seizures was used as endpoint for determining the seizure threshold. The dose necessary to raise or lower the seizure threshold by 50% ($THRD_{50}$) was determined in 4–5 experiments. The $TRRD_{50}$ limit and confidence limit were determined in a regression analysis.

The results of these experiments show that the compound of formula I and its acid addition salts influence functional disturbances of the AMPA receptor. There are therefore suitable for the production of medicines for the symptomatic and preventive treatment of diseases triggered by a change in the function of the AMPA receptor complex.

Diseases which can be triggered by the dysfunction of excitatory amino acids or altered glutamatergic neurotransmission include for example neurodegenerative disorders such as Parkinson's disease, Huntington's disease, Alzheimer's disease, senile dementia, multi-infarction dementia, amyotrophic lateral sclerosis, epilepsy; cell damage by hypoglycaemia, hypoxia, ischaemia and disturbances in energy metabolism; neuronal damage caused by brain injury such as stroke, brain trauma and asphyxia, as well as psychoses, schizophrenia, anxiety states, pain states, migraine and emesis. Functional disorders such as memory disorders (amnesia), disorders of the learning process, vigilance symptoms and withdrawal symptoms following chronic use of addictive substances such as sedative medication, hallucinogenics, alcohol, cocaine and opiates are also based on dysfunction of glutamatergic neurotransmission.

The indications can be demonstrated by conventional pharmacological tests.

The invention also comprises pharmaceutical products containing the said compounds, the production thereof and use of the compounds according to the invention for the production of medicines used for the treatment and prevention of the aforementioned diseases. The medicines are produced by known methods by bringing the active ingredient with suitable vehicles, excipients and/or additives into the form of a pharmaceutical preparation suitable for enteric or parenteral administration. Administration can be undertaken orally or sublingually as a solid in the form of

capsules or tablets or as a liquid in the form of solutions, suspensions, elixirs or emulsions or rectally in the form of suppositories or in the form of injection solutions optionally also usable subcutaneously. Suitable excipients for the desired drug formulation are the inert organic and inorganic supports known to a person skilled in the art, for example water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, etc. Optionally, preservatives, stabilising agents, wetting agents, emulsifiers or salts for altering osmotic pressure or buffers may also be included.

The pharmaceutical preparations can be in solid form for example as tablets, coated tablets, suppositories, capsules or in liquid form for example as solutions, suspensions or emulsions.

Carrier systems that can also be used are excipients near an interface such as salts of bile acids or animal or vegetable phospholipids, but also mixtures thereof, as well as liposomes or constituents thereof.

Suitable for oral administration are in particular tablets, coated tablets or capsules with talc and/or hydrocarbon supports or binders, for example lactose, maize starch or potato starch. Administration can also be undertaken in liquid form, for example as a syrup to which optionally a sweetening agent has been added.

Suitable for parenteral administration are in particular injection solutions or suspensions, especially aqueous solutions of the active compounds in polyhydroxy-ethoxylated castor oil.

The dosage of the active ingredients can vary depending on the method of administration, age and weight of the patient, nature and severity of the disease to be treated and similar factors. The daily dose can be given as a single dose to be administered once, or divided into two or more daily doses. The compounds are housed in a dose unit of 0.05 to 100 mg active substance in a physiologically compatible support. Generally a dose of 0.1 to 500 mg/day, preferably 0.1 to 50 mg/day, is used.

Where the production of the starting compounds is not described, they can be produced in a known manner or similarly to known compounds or methods described here.

The examples below are intended to explain the production of the compounds of formula I:

Example 1

{1-[3-(3-Dimethylaminophenoxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone

265 mg of 3-dimethylaminophenyl is placed in 20 ml acetone, then 265 mg potassium carbonate and 824 mg of (4-fluorophenyl)-[1-(3-methylsulphonyloxypropyl)-4-piperidyl]ketone are added and heated under reflux for 3 hours under argon. After evaporating the organic phase, chromatography is carried out over silica gel with methylene chloride and acetone = 1 + 1. 375 mg of {1-[3-(-dimethylaminophenoxy)-propyl]-4-piperidyl}-(4-fluorophenyl)ketone is obtained.

The (4-fluorophenyl)-1-[1-(3-methylsulphonyloxypropyl)-4-piperidyl]ketone is obtained according to methods known from the literature by alkylation of 4-(4-fluorobenzoyl)piperidine with 3-bromopropanol-1 and potassium carbonate in dimethylformamide and subsequent reaction with methanesulphonic acid and triethylamine in methylene chloride.

The following are produced in a similar manner:
{1-[3-(2-dimethylaminophenoxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(4-dimethylaminophenoxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(3-morpholinophenoxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(1-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(2-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(3-dibutylaminophenoxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(2-nitro-1-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(1-nitro-2-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(2,4-dinitro-1-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone

{1-[3-(3-anilinophenoxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(1-bromo-2-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(4-chloro-2-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(3-acetylaminophenoxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
(4-fluorophenyl)-{1-[3-(5-isoquinolyloxy)propyl]-4-piperidyl}ketone
(4-fluorophenyl)-{1-[3-(3-pyridyloxy)propyl]-4-piperidyl}ketone
{1-[3-(3-dimethylaminophenoxy)propyl]-4-piperazinyl}-(4-fluorophenyl)ketone
(4-fluorophenyl)-{1-[3-(3-(N-methylanilino)phenoxy)propyl]-4-piperidyl}ketone

Example 2

1-{1-[3-(3-Dimethylaminophenoxy)propyl]-4-piperidyl}-1-(4-fluorophenyl)methanol

384 mg of {1-[3-(3-dimethylaminophenoxy)propyl]-4-piperidyl}-(4-fluorophenyl)-ketone is added portionwise at room temperature to a solution of 15 ml ethanol and 80 mg sodium borohydride. After stirring for 4 hours the reaction solution is neutralised, water is added and then extraction performed with ethyl acetate. After drying the organic phase the mixture is concentrated by evaporation and the residue chromatographed over silica gel with acetone + methylene chloride = 1 + 1.

The following are produced in a similar manner:
1-{1-[3-(1-naphthyloxy)propyl]-4-piperidyl}-1-(4-fluorophenyl)methanol
1-{1-[3-(2-naphthyloxy)propyl]-4-piperidyl}-1-(4-fluorophenyl)methanol

Example 3

(3-Dimethylaminophenyl)-{3-[4-(4-fluorobenzyl)-1-piperidyl]propyl}ether

2 g triethylsilane is added dropwise to a solution of 384 mg of {1-[3-(3-dimethyl-aminophenoxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone in 25 ml trifluoroacetic acid. The reaction mixture is stirred for 3 days. Thereafter it is evaporated to dryness and the residue taken up in ether and extracted by shaking three times with 1N HCl. The combined extracts are rendered basic, extracted with ether, dried and evaporated.

197 mg of (3-dimethylaminophenyl)-{3-[4-(4-fluorobenzyl)-1-piperidyl]propyl}ether is obtained.

The following are produced in a similar manner:
1-naphthyl-{3-[4-(4-fluorobenzyl)-1-piperidyl]propyl}ether
2-naphthyl-{3-[4-(4-fluorobenzyl)-1-piperidyl]propyl}ether

Example 4

{1-[1-(3-Dimethylaminophenyloxy)butyl]-4-piperidyl}-(4-fluorophenyl)ketone

630 mg of (4-chlorobutyl)-(3-dimethylaminophenyl)ether in 25 ml dimethylformamide is stirred under argon with 950 mg of 4-(4-fluorobenzoyl)piperidine and 0.5 ml triethylamine for 8 hours at a bath temperature of 100°C. After distilling off the solvent, the residue is taken up in methylene chloride and washed once with water and once with saturated saline solution. The organic phase is dried, filtered and evaporated. The residue is chromatographed over silica gel with acetone and methylene chloride = 1 + 1. 420 mg of {1-[1-(3-dimethylaminophenoxy)butyl]-4-piperidyl}-(4-fluorophenyl)ketone is obtained.
The (4-chlorobutyl)-(3-dimethylaminophenyl)ether required as starting material is obtained by etherification of 3-dimethylaminophenol with 1-bromo-4-chlorobutane and potassium carbonate in dimethylformamide.

Example 5

{1-[1-(3-Dimethylaminophenyloxy)ethyl]-4-piperidyl}-(4-fluorophenyl)ketone

Similar to the method described in Example 4, 590 mg of {1-[1-(3-dimethylaminophenoxy)ethyl]-4-piperidyl}-(4-fluorophenyl)ketone is obtained from 590 mg of (2-chloroethyl)-(3-dimethylaminophenyl)ether and 950 mg of 4-(fluorobenzoyl)piperidine.

Example 6

{1-[3-(3-Dimethylaminophenoxy)-2-hydroxypropyl]-4-piperidyl}-(4-fluorophenyl)-ketone

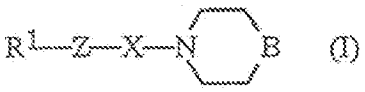
380 mg of (3-dimethylaminophenyl)-(2,3-epoxypropyl)ether is dissolved in 50 ml methanol and 430 mg of 4-(4-fluorobenzoyl)piperidine is added. After heating for three hours the solvent is distilled off, the residue is taken up in 50 ml 1N hydrochloric acid and extracted several times with 1 chloroform. The aqueous phase is rendered alkaline with 2N sodium hydroxide solution and then extracted with ethyl acetate. The combined ethyl acetate phases are washed, dried, filtered and evaporated. The residue is chromatographed over silica gel with acetone and methylene chloride = 1 + 1. 446 mg of {1-[3-(3-dimethylaminophenoxy)-2-hydroxypropyl]-4-piperidyl}-(4-fluorophenyl)ketone is obtained.

The (3-dimethylaminophenyl)-(2,3-epoxypropyl)ether required as starting material is obtained by reacting 3-dimethylaminophenol with epichlorohydrin and sodium hydride in dimethylformamide.

The following are produced in a similar manner:
3-[4-(4-fluorobenzyl)piperidino)-2-hydroxypropyl]dimethylaminoaniline
{1-[3-(3-morpholinophenoxy)-2-hydroxypropyl]-4-piperidyl}-(4-fluorophenyl)-ketone
2-[4-(4-fluorobenzyl)piperidino)-2-hydroxypropoxy]naphthalene
1-[4-(4-fluorobenzyl)piperidino)-2-hydroxypropoxy]naphthalene
{1-[3-(1-naphthyloxy)-2-hydroxypropyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(2-naphthyloxy)-2-hydroxypropyl]-4-piperidyl}-(4-fluorophenyl)ketone

Claims

1. Compounds of the formula I



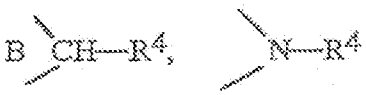
wherein

R^1 stands for substituted or unsubstituted phenyl, substituted or unsubstituted pyridine, substituted or unsubstituted naphthalene, substituted or unsubstituted quinoline, substituted or unsubstituted isoquinoline, substituted or unsubstituted indole, substituted or unsubstituted benzothiophene, substituted or unsubstituted benzofuran, substituted or unsubstituted tetrahydroquinoline, substituted or unsubstituted tetrahydroisoquinoline,

Z stands for oxygen, sulphur, SO or SO_2,

X stands for $-(CH_2)_m-CR^2R^3-(CH_2)_p$,

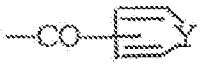
$-(CH_2)_m-CHR^2-(CH_2)_g-CHR^3-(CH_2)_p-$,

 and

m, p and g each stand for 0, 1, 2 or 3,

R^2 and R^3 are the same or different and stand for hydrogen, hydroxy, C_{1-4}-alkyl or C_{1-4}-alkoxy,

R^4 stands for hydrogen, C_{1-6}-alkyl straight-chain or branched,



or a phenyl, benzyl, benzoyl, α-hydroxybenzyl or pyridine residue optionally substituted with C_{1-4}-alkyl, C_{1-4}-alkoxy, halogen, hydroxy, $-CF_3$ or $-O-CF_3$, and

Y stands for oxygen, sulphur or –NH–,

and physiologically compatible salts and isomers thereof.

2. {1-[3-(1-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone

{1-[3-(2-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone

{1-[3-(2-nitro-1-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone

{1-[3-(1-nitro-2-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(2,4-dinitro-1-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
(4-fluorophenyl)-{1-[3-(5-isoquinolyloxy)propyl]-4-piperidyl}ketone
{1-[3-(1-bromo-2-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(4-chloro-2-naphthyloxy)propyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(1-naphthyloxy)-2-hydroxypropyl]-4-piperidyl}-(4-fluorophenyl)ketone
{1-[3-(2-naphthyloxy)-2-hydroxypropyl]-4-piperidyl}-(4-fluorophenyl)ketone
1-{1-[3-(1-naphthyloxy)propyl]-4-piperidyl}-1-(4-fluorophenyl)methanol
1-{1-[3-(2-naphthyloxy)propyl]-4-piperidyl}-1-(4-fluorophenyl)methanol
1-naphthyl-{3-[4-(4-fluorobenzyl)-1-piperidyl]propyl}ether
2-naphthyl-{3-[4-(4-fluorobenzyl)-1-piperidyl]propyl}ether.

3. Medicinal products based on the compounds according to claims 1 and 2.

4. Method for the production of compounds according to claim 1, characterised in that

a) a compound of formula II

R^1–Z–H (II),

wherein R^1 and Z have the meanings disclosed above, is reacted with a compound of formula III

(III)

wherein X and B have the meanings disclosed above and A represents a leaving group, or

b) a compound of formula IV

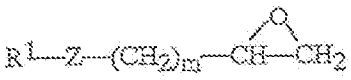
A–X–Z–R^1 (IV),

wherein X, Z and R^1 have the meanings disclosed above and A represents a leaving group, is reacted with an amine of the formula V

(V)

wherein B has the meaning disclosed above, or

c) an epoxide of the formula VI



(VI)

wherein R^1, Z and m have the meanings disclosed above, is reacted with an amine of the formula V

and then optionally a carbonyl group is reduced or the physiologically compatible salts are formed or the isomers separated.

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